Effect of Aminoglutethimide in Adrenal Regeneration Hypertension (34180)

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Aminoglutethimide, 2-(*p*-aminophenyl)-2-ethylglutarimide (AG) is a drug used originally for its effects on the central nervous system as an anticonvulsant. It has some thyroid-inhibiting activity (1–3) and its ability to inhibit steroidogenesis in the adrenal has been well established [(4–6) and others, Rev: (7)]. It interferes with steroid synthesis primarily, but perhaps not exclusively, at some stage prior to the formation of Δ^5-pregnenolone. One potential manifestation of an inhibited adrenal cortical function is the amelioration of hypertensive disease. This report concerns the effect of AG on the syndrome of adrenal regeneration hypertension (ARH) in rats.

Methods. The AG phosphate was given daily in aqueous solution by stomach tube (50 mg/kg; 25 mg/ml). Systolic blood pressure was measured with an E & M Physiograph. The food used was Wayne Lab Blox. Hypertension was produced by the method of Skelton (8). This consists of giving female rats, initially about 135 g of body weight, 1% NaCl solution to drink after enucleation of one adrenal and removal of the remaining adrenal and one kidney. The AG was given from the time of operation for 7 weeks. Pressure readings were taken just before the daily dose of drug.

Results. The blood pressures of drug-treated animals were consistently lower throughout the experiment than controls (Fig. 1). With several drugs studied, we have found only one—hydralazine—which ameliorated the steroid-related hypertensions without at the same time reducing the voluntary intake of 1% NaCl drinking fluid (9). The AG-treated animals, however, generally drank more salt solution than controls, although statistical significance of this difference could not be established (Table I). In any case it is certain that the depressor effect of the drug was not due to depressed salt intake.

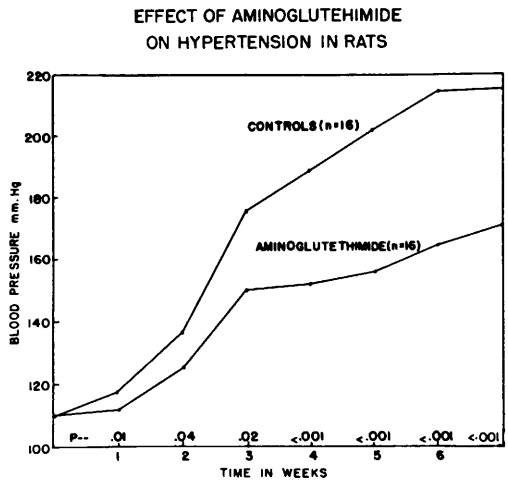

FIG. 1. Effect of aminoglutethimide (50 mg/kg/day p.o.) on blood pressure in adrenal regeneration hypertension. The probability of significant differences (p) for blood pressure values is shown.

The drug caused a marked increase in the weight of enucleate adrenals (Table II), a fact probably due to an inhibition of corticosterone secretion and a consequent increase in ACTH output. In other circumstances, we have found that the corticosterone secretion rate from the left adrenal of normal rats, as determined on blood samples obtained by adrenal vein cannulation, was reduced after each dose of AG (50 mg/kg) to less than one-third normal for at least 6 hr with recovery by 24 hr. Most protective therapies prevent the hypertrophy of kidneys and the heart characteristic of this type of hypertension (9). AG did not do so, a fact possibly related to its failure to reduce salt intake (Table II).

Ovarian enlargement was pronounced in

TABLE I. Saline Intake in Animals Shown in Fig. 1 with Adrenal Regeneration Hypertension.[a]

Groups	Week 1	2	3	4	5	6	7
Controls	40 ± 2.2	54 ± 3.5	69 ± 3.4	84 ± 6.6	88 ± 6.8	82 ± 5.7	82 ± 8.0
AG treated	41 ± 3.7	51 ± 6.6	73 ± 8.2	94 ± 8.9	106 ± 9.9	111 ±10.1	97 ±10.3

[a] (ml/rat/day ± SE).

TABLE II. Body and Organ Weights of Female Rats with Adrenal Regeneration Hypertension Treated with Aminoglutethimide for 7 Weeks (cf. Fig. 1).[a]

Treatment	Body wt (g) Init.	Term.	Organ wt (mg/100 g of body wt ± SE) Enuc. adrenal	Ovaries	Kidneys	Heart	Thyroid
No drug	135	216	18.8 ± 1.2	26.9 ± 1.3	840 ± 82	459 ± 17	6.8 ± 0.45
AG, 50 mg/kg/day	138	235	30.4 ± 2.5	45.6 ± 2.3	934 ± 96	452 ± 15	7.3 ± 0.30
p (treated vs. no drug)			<.001	<.001	NS	NS	NS

[a] (n = 16 rats per group).

drug-treated animals as others (10) have seen before, suggesting an inhibition in estrogen synthesis. For reasons not known, perhaps one of dosage, the expected (1–3) thyroid hypertrophy was not observed (Table II).

Discussion. The idea is growing in acceptance that in addition to the known deficiencies of adrenal function after enucleation, some steroid(s) is excreted in excess and that it is the direct cause of the adrenal contribution to ARH. This may be an excess of 11-desoxycorticosterone (11), 18-OH-desoxycorticosterone (12) or possibly the unidentified factor particularly evident in tests early after enucleation which cause intense Na-retention (13). That AG inhibits corticosterone and aldosterone secretion would not be expected to have an antihypertensive effect in this syndrome since corticosterone is clearly not its cause (14) and aldosterone secretion is reduced in regenerate adrenals and particularly so when a high sodium intake is involved. It is, therefore, more probable that AG was active as an antihypertensive in our cases because it inhibited the secretion of an as yet unidentified steroid(s) causing the hypertension.

Thyroid deficiency induced by the drug theoretically could also have been a factor in ameliorating the hypertension. This is unlikely, however, because had any marked thyroid deficiency been caused with the dosage and under the conditions used here, it should have been manifest by an increase in thyroid weight. This did not occur (Table II). AG has also been found useful in various types of human hypertension associated with adrenal dysfunction (15, 16). The mechanisms involved in human and animal observations may well be identical.

Summary. Aminoglutethimide, when given by stomach tube daily to rats for 7 weeks beginning immediately after adrenal enucleation, reduced markedly the development of adrenal regeneration hypertension. This effect was not due to a reduction of intake of salt drinking solutions. Relative to controls, the drug did not influence renal, cardiac, or thyroid weights. It is postulated that the drug inhibited the secretion of an as yet unidentified steroid that causes adrenal regeneration hypertension.

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